Refer to: Ockner RK: Drug-induced liver disease—Medical Staff Conference, University of California, San Francisco. West J Med 131:36-45, Jul 1979

Drug-Induced Liver Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for this staff conference is drug-induced liver disease. Dr. Henry Kahn, the chief medical resident, will present the first case.*

DR. KAHN:† A 45-year-old white woman was admitted to hospital at the University of California, San Francisco, (UCSF) on July 19, 1978, for evaluation of jaundice. In March 1978 she had presented with fever, pancytopenia and hepatomegaly. Cultures of sputum, pleural fluid, bone marrow and liver biopsy specimens grew Mycobacterium kansasii. Before treatment, the serum glutamic oxaloacetic transaminase (SGOT) was reported at 150 U per ml, the lactic acid dehydrogenase (LDH) was 1,420 U per ml and the alkaline phosphatase was 500 IU per liter. Treatment with isoniazid, ethambutol and rifampin was begun. By June 1978 the patient's condition was clinically improved, with the following values noted: SGOT, 28 U per ml: LDH, 177 U per ml; alkaline phosphatase, 265 IU per liter, and total bilirubin 0.6 mg per dl. In July 1978 she began to note weakness, anorexia, weight loss and jaundice, and administration of isoniazid and rifampin was discontinued. She was referred to UCSF at that time.

Her past history and family history showed moderate use of alcohol, and that a cousin had disseminated Mycobacterium intracellularis. On physical examination, the patient was cachectic and afebrile, with a blood pressure of 105/80 mm of mercury and a pulse of 95. There was scleral and cutaneous icterus, a tender liver enlarged to 14 cm in span and 2+ pitting edema.

Laboratory data showed the following: leukocyte count, 5,200; hematocrit, 23 percent; SGOT, 74 U per ml; LDH, 78 U per ml; alkaline phosphatase, 137 IU per liter; albumin, 2.4 grams der dl, and hepatitis B surface antigen, negative. An x-ray study of the chest done on admission showed resolving bilateral infiltrates.

Administration of rifampin was restarted on July 19, 1978. An extensive workup was done which included a liver-spleen scan, abdominal sonogram and a computer tomography (CT) scan of the liver. These disclosed only hepatomegaly. Without the isoniazid, by July 24 the patient's SGOT level had fallen to 12 U per ml, LDH was 89 U

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per ml, alkaline phosphatase was 91 IU per liter and bilirubin was 3.8 mg per dl. At that point she felt improved. On July 25, however, the temperature rose to 40°C (104°F). All routine cultures were negative; the leukocyte count fell to 2,400, and ultimately to 1,300. X-ray films of the chest showed increasing infiltrates. This was all felt to be consistent with reactivation of the underlying disease, and on August 3, because the question of isoniazid toxicity was unclear, administration of the drug was started again. On August 7 liver function tests showed SGOT to be 300 U per ml; LDH, 200 U per ml; alkaline phosphatase, 140 IU per liter, and total bilirubin, 10 mg per dl. Isoniazid administration was discontinued on August 8. Cycloserine therapy was instituted at that point. When the patient was last seen in the clinic on September 12, symptoms had improved on the regimen of cycloserine, ethambutol and rifampin. The leukocyte count remained low at 1,900, hematocrit was 34 percent and platelet count was 90,000. Liver function tests showed SGOT to be 25 U per ml; LDH, 159 U per ml, alkaline phosphatase, 140 IU per liter, and total bilirubin 2 mg per dl.

DR. SMITH: *We have a second brief case for presentation. Dr. Ann Hritz will summarize it.*

DR. HRITZ:* A 23-year-old black woman was admitted to the UCSF hospital on October 18, 1978, for evaluation of seizures, fever, pneumonia, dermatitis, hepatitis and anemia. In August 1978 she had presented at another hospital with a right upper lobe infiltrate which resolved on treatment with amoxicillin given orally. She was readmitted in September 1978 with grand mal seizures. A lumbar puncture and brain scan showed no abnormalities. She was treated with diphenylhydantoin and phenobarbital. It is of note that results of liver function tests at that time were within normal limits.

In October 1978 the patient was seen again at the other hospital for seizures, fever, exfoliative dermatitis, lymphadenopathy and hepatomegaly. The SGOT level was 544 U per ml, the bilirubin value was 4.8 mg per dl and the hematocrit had dropped from 38 percent to 23 percent without evidence of bleeding. A new right upper lobe infiltrate was noted which did not resolve on treatment with broad spectrum antibiotics.

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Her past medical history included atopic dermatitis since childhood and a character disorder. There had been no head trauma, hepatitis, use of drugs other than the diphenylhydantoin and phenobarbital, or ethanol abuse.

On physical examination, after transfer to UCSF, the patient was noted to be obese, with generalized erythroderma and exfoliative dermatitis. She was tachypneic with audible wheezing. Blood pressure was 90/70 mm of mercury; pulse, 120; respiratory rate, 50, and temperature, 39.9°C (103.82°F). Generalized subcutaneous edema, erythroderma and exfoliative dermatitis sparing only the mucous membranes were present. Right posterior cervical adenopathy was noted. On examination of the chest, there was at the base of both lungs dullness with decreased breath sounds. Rales were heard posteriorly over the right lung field, and there were diffuse wheezes and rhonchi. Cardiac examination showed a 2/6 systolic ejection murmur along the left sternal border. The patient's liver was tender and enlarged to 14 cm in span, and there was no evidence of splenomegaly. She was disoriented and combative. Findings on neurological examination were normal except for bilateral ankle clonus.

Laboratory studies gave the following values: the leukocyte count was 35,900 with 48 polymorphonuclear lymphocytes, 4 bands and 11 eosinophils; hematocrit, 26.2 percent; platelet count, 155,000; prothrombin time, 37.6 seconds, and partial thromboplastin time, greater than 100 seconds. A disseminated intravascular coagulation screen was negative. Results of renal function tests were normal and the blood glucose value was 43 mg per dl. The calcium level was 6.6 mg per dl; phosphorus, 0.6 mg per dl; albumin, 2.2 grams per dl. SGOT was 380 U per ml; alkaline phosphatase, 130 IU per liter; LDH, 584 U per ml, and bilirubin, 11.8 mg per dl. An x-ray film of the chest showed a left lower lobe, a right lower lobe and a right upper lobe infiltrate, and a Gram stain showed rare polymorphonuclear leukocytes with mixed oral flora.

The patient was treated with ampicillin and gentamicin and the pulmonary infiltrates resolved, although sputum cultures were not diagnostic. The dermatitis cleared after topical application of steroids. The hepatitis gradually improved after administration of diphenylhydantoin and phenobarbital was stopped. Prothrombin time also improved with fresh frozen plasma and vitamin K

administration. Findings on a liver biopsy were compatible with resolving acute hepatitis. The patient's course was further complicated by transient agranulocytosis and acute nonoliguric renal failure which resolved before discharge. There were recurrent seizures with a left temporal lobe focus, shown on an electroencephalogram, which were successfully treated with phenobarbital alone. She was discharged on November 22 without evidence of a drug reaction to the present anticonvulsant regimen. At discharge the SGOT level was 80 U per ml; alkaline phosphatase, 120 IU per liter; bilirubin 9 mg per dl, and prothrombin time and partial thromboplastin time within normal limits.

DR. SMITH: *Thank you very much. We would like to call on Dr. Robert K. Ockner to discuss these complex problems and more generally the question of drug-induced liver disease.*

DR. OCKNER:* The two cases presented illustrate very well many aspects of the common and important problem of drug-induced liver disease. It is a very difficult problem for several reasons. First, when adverse events occur during treatment with a drug for some illness, it often is unclear whether one is dealing with a reaction to the drug, an exacerbation of the underlying process or an entirely unrelated event. Second, not only are many agents in common use suspect, but every new agent that appears must be considered. Third, the matter of diagnosis is further confused by the nonspecificity of the histopathology of most drug-induced lesions; with a very few exceptions, they may closely mimic virtually all forms of liver disease. Finally, because of the tremendous number and diversity of the drugs that have been implicated and the reactions that can be seen, it is difficult to review this subject and not have it read a bit like a catalogue. To avoid this particular pitfall I briefly will review the spectrum of disorders that are associated with drug-induced liver disease, make some more detailed comments on those that are especially instructive or otherwise important for clinical or theoretical reasons, and finally comment on the two cases presented. While the lesions in these cases have histological similarities, the cases are obviously very dissimilar clinically. I reviewed this subject at these rounds about three years ago. Since that time a number of concepts that were current then have stood the test of time, but others certainly have been called into question and new concerns and problems have been raised.

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TABLE 1.—*Drug-Induced Liver Injury: Clinical-Histopathological Patterns and Examples*

Zonal necrosis (acetaminophen)
Acute viral hepatitis-like reactions (isoniazid, diphenylhydantoin)
Chronic hepatitis (methyldopa)
Cholestasis
with inflammation, necrosis (chlorpromazine)
without inflammation, necrosis (estrogens)
Fatty liver
Large vacuoles (ethanol)
Small droplets (tetracycline)
Granulomata (allopurinol)
Tumors (oral contraceptives)

There are many ways to classify drug-induced liver disease. Most of the standard reference sources that deal with this topic simply list agents on the basis of their pharmacological properties—as hormones, antibiotics and the like—and then deal with the kinds of reactions that may be associated with individual drugs in each category.[1,2] That approach is particularly useful to identify the possibilities in a given case. It is perhaps less useful as the basis for today's discussion because I will review more general principles and some of the mechanisms involved. The classification I will employ is based both on histopathology and what is known (meager as it may be in some cases) about the mechanism of the injury itself. This classification is given in Table 1, and for each type of reaction one or two drugs are presented as examples.

In zonal necrosis, the first category, injury is limited to, or especially prominent in, one portion of the liver lobule. For example, central necrosis is characteristically produced by so-called *direct toxins* such as acetaminophen and carbon tetrachloride. Acetaminophen is of considerable importance clinically, and we will return to consider it at greater length. Reactions in this category are generally predictable, often dose-related, and can be produced in experimental animals. The agents of concern in the case summaries presented here fall into the category of viral hepatitis-like reactions. Unlike the first category, these agents produce necrosis which usually is focal but may be submassive or massive, rather than zonal. They are neither predictable, nor apparently dose-

related, and rather seem to depend on some kind of host idiosyncrasy, the nature of which is not well understood in most instances.

The third category, chronic hepatitis, serves as a reminder that this broad group of syndromes of chronic liver inflammation includes cases in which an etiologic role of certain drugs has been well documented; these will be mentioned briefly later in the discussion.

Cholestasis—that is, impairment of bile flow—includes two general categories: those associated with inflammation and necrosis, and those in which these features are lacking. The first group is exemplified perhaps best by chlorpromazine, and includes a very large number of other agents as well. Those forms of drug-induced cholestasis not generally associated with inflammation and necrosis are typified by the estrogens, oral contraceptives and anabolic steroids. Fatty liver also can be divided into two subcategories on the basis of the histopathology. First, there are those conditions in which fat is deposited in large vacuoles, so that the liver cell takes on the appearance of an adipocyte because of the substantial displacement of the nucleus. This is the typical appearance of fatty liver caused by ethanol abuse, as well as obesity, corticosteroid treatment and protein-calorie malnutrition. In contrast, the second group of conditions is associated with deposition of fat in small droplets distributed throughout the cell, while the nucleus remains centrally located. The classic example is the reaction caused by high doses of intravenously given tetracycline, but it is also very similar to other conditions which apparently are not drug-related, such as the Reye syndrome, obstetrical fatty liver and Jamaica vomiting sickness.

It should be noted that the most important difference between these groups with fatty liver is not so much in the histopathology, but rather in their clinical presentation. In the first group, the findings are largely unimpressive, apart from hepatomegaly and abnormal results on liver function tests, and there is no evidence that the fat in those conditions produces substantial long-term injury. In contrast, the second group is characteristically associated with a presentation that is very suggestive of massive liver cell failure and often carries a very high mortality rate. Granulomata are caused by perhaps half a dozen drugs such as phenylbutazone, phentoin, quinidine and allopurinol. Finally, hepatic tumors are included because of current concerns about their possibile relationship to oral contraceptives.

I would emphasize that the above list is not comprehensive, and certain forms of tumors and vascular occlusive processes have been excluded. Moreover, a number of drugs may cause more than one kind of reaction, while in a given patient elements of more than one kind of histopathologic change may be seen. Therefore, these categories are not necessarily rigid, specific or exclusive, either for the drug or the patient. Rather, they are intended to provide a conceptual framework.

Zonal Necrosis

Acetaminophen is of importance because it is perhaps the best understood of the agents that we will consider today. It is readily available, and has been used with increasing frequency in suicide attempts. To the extent that it succeeds, it causes a liver death, and usually requires acute ingestions in excess of 10 grams.[3] Recently, however, it has been appreciated that sustained use of acetaminophen in doses in excess of 3 grams per day may also be associated with chronic low-grade, benign and reversible liver injury.[4] The liver lesion seen in the acute cases is centrilobular necrosis, and these patients either die in the acute episode or recover completely. There is no evidence that a single exposure to acetaminophen can initiate chronic liver injury. Mitchell and his colleagues have developed much of the current information about the mechanism of acetaminophen hepatotoxicity.[3] In experimental animals it has been shown that phenobarbital, a potent inducer of drug metabolizing enzyme systems in the smooth endoplasmic reticulum, increases the rate of acetaminophen metabolism and also its toxicity. In contrast, agents that block acetaminophen metabolism are protective. The rate of metabolism of the parent compound correlates directly in those studies with covalent binding of an apparently toxic metabolite of acetaminophen to cell macromolecules, and also with the extent of liver cell necrosis. So, the concept advanced on the basis of those studies was that a toxic metabolite, rather than the parent compound, is responsible for the liver cell injury. The metabolism of acetaminophen is summarized in Figure 1. Normally a large amount is conjugated and excreted in urine, but some may be metabolized by the cytochrome P-450 dependent systems in the microsomes. To some extent the products of this latter pathway will be conjugated with glutathione and excreted

without ill effect. When large amounts are formed, however, some will react with cell macromolecules and, apparently through that mechanism, initiate a sequence that results in cell death.

Mitchell and his co-workers also have shown that as long as the cellular concentration of glutathione is adequate, the animal remains relatively protected from the effects of acetaminophen. However, as the acetaminophen dose increases, glutathione is consumed and falls to a critical level, at which the covalent binding of toxic metabolite to cell proteins increases exponentially. It should be noted that "covalent binding" per se has not been clearly established as the cause of cell injury; there are circumstances in which cells may be protected against toxic injury without an effect on covalent binding.[5] Nonetheless, this interesting concept has been useful in two general ways. First, it has provided an explanation for the threshold phenomenon in this form of toxic liver injury. Second, it suggested the possibility that if endogenous sulfhydryl groups serve a protective function, then perhaps exogenous sulfhydryl donors might be useful in the treatment of patients with acetaminophen overdosage. Of several agents that have been tested, two of the more prominently employed have been cysteamine and N-acetylcysteine. Cysteamine has been studied in greatest detail by Prescott and his associates in Edinburgh and has been the subject of considerable debate.[6] I believe it is fair to say that, despite its own substantial toxicity, the available evidence tends to support Prescott's contention that cysteamine may be protective when given early in the course to patients with significant acetaminophen overdosage. However, this interpretation is not uniformly accepted and the role for this agent remains unclear. Moreover, to the extent that cysteamine may, in fact, be beneficial, available experimental data suggest that it does not act as a sulfhydryl donor in the sense that it becomes covalently linked to the acetaminophen metabolite, but rather must act via some other mechanism, perhaps by influencing the rate of drug metabolism. At present, much more attention is focused on N-acetylcysteine, which is the subject of a national multicenter study. Results of that study are still inconclusive, but this agent has the

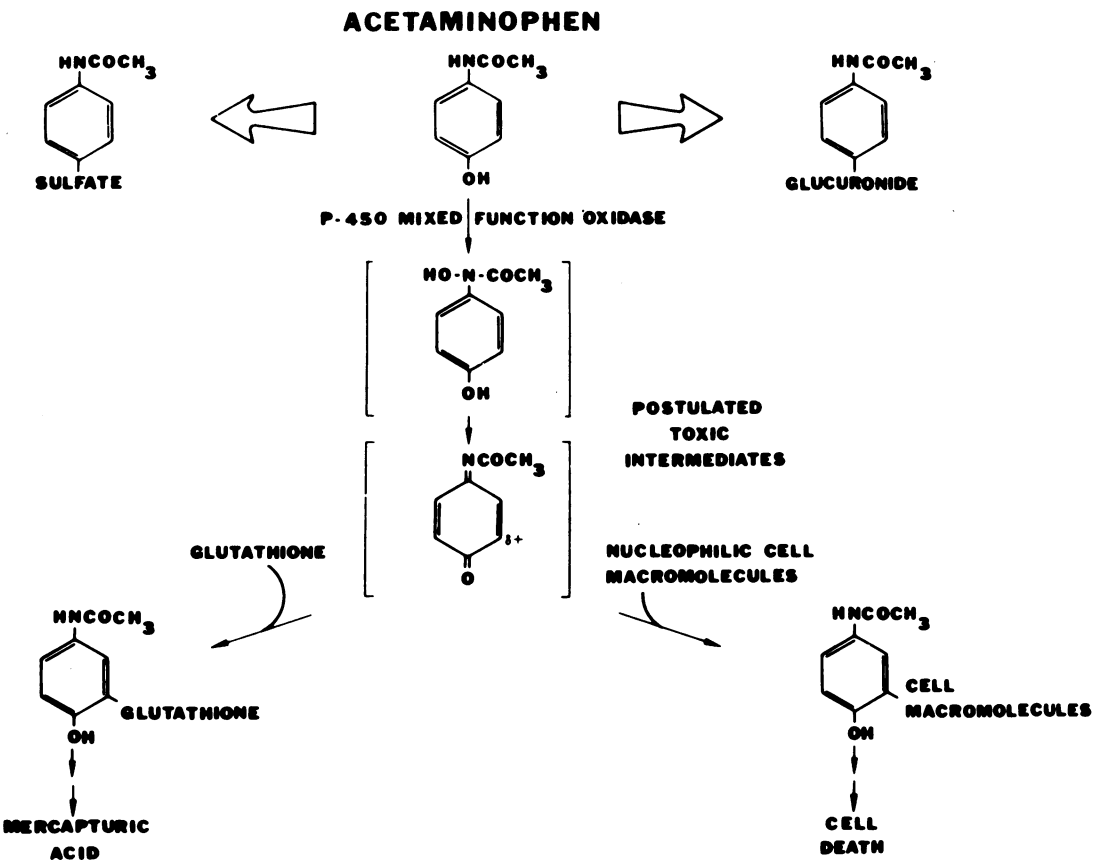

Figure 1.—Acetaminophen metabolism (reproduced with permission from Mitchell JR, and *Gastroenterology*[3]).

distinct advantage of apparently being nontoxic. There have been some favorable anecdotal reports regarding its role in the treatment of acetaminophen overdose.[7]

Chronic Hepatitis

The fact that chronic hepatitis can be caused by drugs has now been well documented.[8] Oxyphenisatin, while no longer available in this country, is available elsewhere, as an ingredient of certain laxative preparations. Other agents still in use can also cause this syndrome, including methyldopa, isoniazid, certain sulfonamides and, as mentioned, acetaminophen. Aspirin in doses in excess of about 3 grams a day may also produce continuing liver injury, perhaps analogous to that caused by chronic acetaminophen use in that both appear to be entirely reversible on cessation of therapy.[9] Alcohol can also cause a form of chronic hepatitis which is not necessarily associated with other, more typical features of alcoholism. It is important to keep in mind that these, and perhaps other drugs as yet unrecognized, should be considered in the differential diagnosis of patients with chronic liver disease.

Cholestasis

Cholestatic reactions, as noted, are of two general types. The first of these is not associated with hepatic inflammation, is entirely reversible and appears somewhat dose-dependent, and similar kinds of changes can be produced in laboratory animals. It seems likely that this reaction represents a *toxic* effect of the steroid on some aspects of liver cell function, the possible nature of which we will return to shortly. Agents which cause this form of cholestatic injury include natural and synthetic estrogens, the oral contraceptives, and anabolic and androgenic steroids which bear alpha-substituted groups at the 17 carbon of the steroid nucleus. The classical example of this reaction is seen in a few patients in whom frank jaundice develops while they are taking oral contraceptives or during the later phases of pregnancy.[10] Although the response is somewhat dose-dependent, there is an important *host* determinant of susceptibility that is not understood. It is not based on allergy, but perhaps may involve the production of unusual drug metabolites or interactions of steroids with cell membrane constituents. In some patients, these agents appear to unmask a previously inapparent Dubin-Johnson syndrome.

TABLE 2.—*Drug-Induced Cholestasis: Postulated Mechanisms and Examples*

1. Interference with specific solute transport systems (rifampin)
2. Inhibition of Na^+, K^+ adenosinetriphosphatase (chlorpromazine metabolites)
3. Alteration of membrane physical properties (estrogens)
4. Effect on microfilaments (phalloidin)
5. General interference with liver cell energy production

The second group of drugs that cause cholestasis produces an inflammatory lesion, often associated with necrosis. This category is much broader, and includes many very commonly used agents such as tranquilizers, diuretics, antithyroid agents, oral hypoglycemics and certain antibiotics. As a group, reactions tend to be less predictable, and more idiosyncratic in that they seem to depend on pronounced individual differences in susceptibility. Although this has been interpreted as suggesting that these are allergic drug reactions, this concept has not been proved. Moreover, in the case of chlorpromazine, it is recognized that among patients who take large amounts of this agent over long periods, there is a substantial incidence of abnormal findings on liver function tests, suggesting that the impairment of bile secretion may be more predictable and dose dependent than has been assumed. Evidence in support of this concept has been developed in recent studies by a number of groups. Suffice it to say that a number of derivatives of chlorpromazine have potent *direct* and predictable effects on various aspects of the bile secretory process. For many other drugs that cause cholestatic injury, the superficial appearance of *allergy* (that is, rash, fever and eosinophilia) may not be inconsistent with liver injury which is, in fact, toxic in its pathogenesis.

How is it possible for this diverse array of agents to interfere with bile secretion and, in so doing, to often mimic biliary tract obstruction? A few suggested mechanisms are listed in Table 2; there are others as well. It is possible that some agents may interfere with specific solute transport systems. For example, there is evidence in man and experimental animals that rifampin has a direct and reversible effect on hepatic uptake processes, possibly mediated at the cell membrane. A number of agents interfere with the function of liver cell membrane Na^+, K^+ adenosinetriphosphatase. The nature of the relationship

of this enzyme to bile secretion is still a matter of investigation, but it has been shown to be sensitive to agents that are associated with cholestasis. Estrogens and other agents have been shown to alter the physical properties of the membrane, usually associated with changes in fluidity. Recent evidence in regard to phalloidin, a toxin in the poisonous mushroom Amanita phalloides, has shown that this agent interferes with normal microfilament function, and it has been suggested that it may cause cholestasis experimentally through its effect on cytoskeletal elements. Finally, a cholestatic syndrome can result from a very nonspecific interference with cell energy production. Although not a drug-related phenomenon, it is worth mentioning that in patients in whom the liver has been severely anoxic—for example, in cases of prolonged hypotension or severe congestive failure—a frankly cholestatic syndrome resembling bile duct obstruction may occur. This suggests that a very nonspecific injury may also profoundly impair bile secretion, implying that this particular response to liver injury may represent a final common path through which a wide range of seemingly unrelated influences may exert an adverse effect.

Hepatic Tumors

The final subject that deserves some comment before we discuss today's cases is the matter of oral contraceptive-associated hepatic tumors.[11] The possible clinical significance of this has been appreciated only since the early 1970's, and recently there has been a flood of case reports and reviews of the subject. It now appears that several hundred cases have been documented, although some of those may have been reported more than once. The actual number of cases therefore is not known, but it probably does not exceed a few hundred. This suggests that we are dealing with what is probably a very rare complication of oral contraceptive use, although its true incidence is certainly not known at present. Most of these tumors are adenomas or focal nodular hyperplasia and, much less commonly, hepatocellular carcinoma. Most of these lesions have been seen in women who have been using oral contraceptives for more than five years, although some have been reported after shorter intervals. There is some suggestion that mestranol might especially predispose to this, but since mestranol has been in use longer than many of the other estrogenic components of the pill, that association may be entirely fortuitous.

One of the factors that makes it difficult to determine the true incidence of this complication of the pill is that it also occurs in nonusers, especially women of childbearing age, as well as in men. The tumors in these groups seem to differ, however, in that they tend to be smaller and less vascular. In a number of cases it now has been well documented that the tumors may regress when use of the oral contraceptive agent has been discontinued. Therefore, there seems little doubt that the pill either produces these lesions, or at least aggravates them.

The presentation of these lesions in a substantial number of cases is dramatic and unexpected. Many present catastrophically, either as hemorrhage into the tumor or into the free peritoneal cavity. This is especially the case with adenomas. Others, especially focal nodular hyperplasia, are discovered only incidentally at laparotomy done for unrelated reasons. The number that are detected by careful physical examination or on the basis of more mild symptoms is small. Moreover, routine liver function tests are disappointingly insensitive, so that more invasive, costly or dangerous tests would need to be employed to detect these lesions with any degree of sensitivity in asymptomatic persons. Obviously, any serious attempt at surveillance would require substantial expense and possible adverse effects, and would not appear to be appropriate. Because of the apparent rarity of these lesions, the priority, as Klatskin has suggested, is to better document its true incidence and to identify other possible etiologic factors rather than to embark on any widespread efforts at screening patients taking oral contraceptives with regard to the possibility that they may have an undiscovered tumor.

Viral Hepatitis-like Reactions

At this point, I would like to turn to the hepatic reactions that resemble acute viral hepatitis and which are exemplified by our two patients today. In addition to isoniazid and phenytoin sodium, this lesion is produced by a number of drugs, including halothane and certain sulfonamides. It is a very important problem for two reasons. First, these reactions are neither predictable nor apparently dose-related, yet unlike most of the other conditions we have discussed, they may often lead to death. Second, they make up a spectrum in themselves in regard to clinical

presentation, which is strikingly shown by the two cases presented in this conference.

Diphenylhydantoin hepatitis has been the subject of some 20 case reports, in a large percentage of which the patients died.[12,13] This undoubtedly reflects some selection so that neither the true incidence of the disease or its prognosis is known. Among the cases reported there does appear to be a somewhat increased incidence among blacks, but again the validity of that impression is not clear.

The first case discussed here fits the general characteristics of the reported cases. The timing of the onset of disease in this patient was entirely consistent with what has usually been observed (that is, two to six weeks after initiating treatment), and she presented with features which suggested an allergic reaction, including erythematous maculopapular eruption, arthralgias and arthritis, fever, lymphadenopathy and a very high eosinophil count. Also, the total leukocyte count was very high, a common observation among the reported cases. The results of liver function tests were abnormal, consistent with an acute hepatic injury; a feature common to many of the reports is a very high prothrombin time. The biopsy findings were entirely consistent with an acute hepatitis-like reaction. The mechanism of this injury is not understood. As noted, the clinical features suggest an allergic reaction and there has been evidence for a circulating antibody to phenytoin sodium in a few of these cases. Its role in pathogenesis is not known, and the mechanism of the liver injury is quite unclear. For example, in several reported cases, patients have been rechallenged with phenytoin sodium after their illnesses have subsided. In these cases, the features of their *allergic* presentation were reproduced by this maneuver, including rash, fever, eosinophilia and sometimes the adenopathy. However, in no case to my knowledge did rechallenge cause any change in liver function. Second, a number of studies have shown that among groups of patients taking this agent for long periods, there is an increased incidence of abnormal results in liver function tests, again suggesting a possible toxic mechanism. In any case, this patient's outcome has been generally favorable. The biopsy features do not imply a chronic hepatitis or other progressive liver injury. The patient had what seemed to be an inappropriately high bilirubin level at one point in the course, and there was a level of 60 mg per dl at a time when clinical improvement

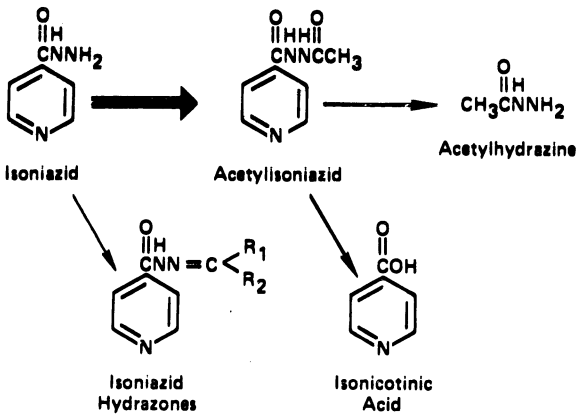

Figure 2.—Metabolism of isoniazid (reproduced with permission from Mitchell JR, and *Ann Intern Med*[14]).

was occurring. There appears to be no obvious single explanation for this. One can only assume that this represented a multifactorial phenomenon, in which residual liver dysfunction, a low-grade hemolysis and some degree of azotemia interfering with the excretion of conjugated bilirubin may all have played a role.

The second case may represent an example of isoniazid-induced liver injury, but is atypical in certain respects. It also illustrates the problem of determining whether an adverse turn of events in a patient's course is due to the disease being treated or to the treatment being used. The seriousness of the infection in this case required certainty about whether isoniazid was indeed toxic. Although rechallenge with isoniazid should generally be avoided, this was an unusual situation that I believe justified the decisions that were made. Usually, the presentation of clinically apparent isoniazid hepatitis is similar to that of viral hepatitis.[14] It is almost never associated with the *allergic* features that characterize phenytoin hepatitis. The onset is usually early, within the first two months, but may occur as late as 12 months. In contrast to phenytoin hepatitis, the incidence of isoniazid hepatitis consistently approximates 1 percent. Also, it is highly age-dependent: among persons younger than 20 it is very rare, rising to about 2 percent among patients older than 50. The reason for this age dependency is not understood. The mortality rate has varied, but is substantial, much higher than for ordinary viral hepatitis, and ranges between 10 percent and 20 percent.

In an earlier study, analyses were done in a group of survivors of isoniazid hepatitis with respect to acetylator phenotype—that is, the rate

at which isoniazid was acetylated (inactivated). From that study it was found that patients with rapid acetylators were disproportionately represented among this group, and it was concluded that they were at increased risk of development of isoniazid hepatitis. This conclusion was quite consistent with the general concept that a toxic metabolite of isoniazid might be responsible for the injury, based on what was known about the drug's metabolism (Figure 2). Isoniazid is first acetylated in the liver, and is thereby inactivated in regard to antibacterial effect. It then is hydrolyzed, and one of the important reaction products is monoacetylhydrazine which is generally accepted to be a potent hepatotoxin. Presumably, then, in persons with rapid acetylators monoacetylhydrazine is produced more rapidly than in persons with slow acetylators. However, the question of whether persons with rapid acetylation are predisposed to isoniazid hepatitis has been reexamined, and at present there is uncertainty about this point. This is because recent studies have shown that monoacetylhydrazine is itself acetylated, and more rapidly so by persons with rapid acetylators. Therefore, while persons with rapid acetylators produce more of the toxin they also inactivate it more rapidly to the less toxic diacetylhydrazine.[15] Consequently, it is possible that individual predisposition to isoniazid hepatotoxicity may be based on factors other than the rate of isoniazid acetylation.

It is important to realize that isoniazid also may produce changes in liver function that are subclinical. These changes differ from those associated with overt hepatitis in several respects. It occurrs in children and it is uniformly agreed that there is no relationship to acetylator phenotype. Laboratory and histological changes are mild, and reversible. The association with symptoms is inconstant, and has proved disappointing in assessing patients with regard to hepatotoxicity.[16] In general, liver function in these patients will return to normal despite continuation of therapy with the drug. The question of whether liver function tests should be routinely done in patients taking isoniazid is still controversial.

All of the studies that I have mentioned in regard to isoniazid have concerned persons receiving single drug chemoprophylaxis. There also are many studies that deal with the question of multiple drug therapy for active disease. This is a very complicated subject, and one that has been reviewed recently.[17] One agent that has received particular attention in this regard is rifampin because it has been suggested that its use is associated with a more fulminant course of hepatitis in patients who are also receiving isoniazid.[18] Current knowledge about the effects of rifampin can be summarized as follows: First, it produces a reversible impairment of hepatic uptake processes, apparently through an effect at the liver plasma membrane. Second, it is an inducer of microsomal drug metabolizing enzymes, and because of that it has been suggested that it may increase the rate of isoniazid metabolism and thereby predispose to isoniazid hepatotoxicity or increase the severity of the reaction when it occurs. Third, rifampin-associated hepatitis has been reported, but almost always in patients who are also receiving isoniazid; the incidence of truly rifampin-induced hepatitis—indeed, its existence—is unknown at present.

In conclusion, it is difficult, given this diversity of drugs and reactions, to provide generally applicable statements. Although diagnosis is probably most reliably accomplished by means of rechallenge, this approach is generally best avoided for those agents that are known to produce fatal reactions. As for the treatment of drug-induced liver disease, this primarily involves discontinuation of the suspected drug or drugs, and supportive care. I am aware of only two instances in which other forms of intervention may be beneficial. The first of these is the use of cysteamine or N-acetylcysteine in the treatment of acetaminophen overdose and, as noted, this remains controversial. The second is partial hepatic resection for oral contraceptive-associated hepatic tumors. There is no firm evidence that corticosteroids are of value in the treatment of the inflammatory viral hepatitis-like or cholestatic hepatic drug reactions, although they may be employed when systemic allergic features are particularly severe and threatening. It is clear that in this complex area substantial challenges remain, ranging from chemistry and pharmacology to clinical medicine. In the meantime we can deal best with the problem by being alert to it as an important cause of liver disease generally, and an important aspect of the continuing evaluation and management of the individual patient.

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Optimal Hematocrit

WHEN DO YOU give red cells? What is the obtimal hematocrit for a sick patient? The answer is, of course, I do not know, but there are some indications. It ought to be higher in somebody who is going to face stress on the oxygen delivering system. It should certainly be higher in somebody who has impaired hemoglobin functions so that he cannot compensate. Somebody who has been extensively transfused with old stored blood has impaired red cells, and that patient is going to require a higher hematocrit than somebody who has not been extensively transfused or who has been given fresher blood. . . .

There are possibly some situations where you might get by or might even favor a lower hematocrit. . . . The most important factor on the side of lower hematocrit is low demand. If patients are not facing a disaster, if the hemorrhage is over, if they are doing well, if they are tolerating their level of anemia well for what they are doing at the time, then for heaven's sakes leave them alone—do not transfuse them. Transfusion carries with it a significant risk. . . . If the challenge is over, and the patient is doing well, do not treat a number, treat the patient. This business of having everybody at a hematocrit of 30 because somebody says that's the right number is a silly thing. An example might be a kid who has been speared in a hockey game, is 19 years old—a young, healthy buck—has a ruptured spleen, has a quick splenectomy before the blood arrives, is awake and alert and doing very well that evening in the recovery room, asking for the newspaper, and has a hematocrit of 19. That kid should not be transfused unless you think the tie is going to come off one of your vessels, in which case you should probably reoperate and put on the damn tie properly. Do not treat numbers—treat patients.

On the other hand, let us say we have a 72-year-old woman who had a perforated diverticulum, had pus and stool all over the abdomen. She had a myocardial infarction that was known three years ago; she has an electrocardiogram suggesting several others; she's been on digitalis; she came out of a nursing home depleted, and she has an hematocrit of 32. That patient requires red cells, especially if she's having ventricular premature contractions on the monitor. Just like everything else in clinical medicine, it has to be individualized.

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Extracted from *Audio-Digest Surgery*, Vol. 26, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206